

Complete Summary

GUIDELINE TITLE

Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Noble J, Ellis P, Mackay JA, Evans WK, Lung Cancer Disease Site Group. Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Mar 27. 51 p. (Evidence-based series; no. 7-19). [89 references]

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Recurrent or progressive non-small-cell lung cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate the survival and/or quality of life (QOL) benefits of systemic therapy compared with best supportive care (BSC) in the second-line and subsequent treatment of recurrent or progressive non-small cell lung cancer (NSCLC)
- To evaluate which systemic therapy agent or combination of agents provide the greatest improvement in survival and/or QOL in the second-line and subsequent treatment of recurrent or progressive disease
- To evaluate the optimal doses and schedules of different systemic therapy agents in the second-line or subsequent treatment of recurrent or progressive disease

TARGET POPULATION

Adult patients with advanced or metastatic non-small cell lung cancer (NSCLC) that has recurred or progressed following prior systemic therapy

INTERVENTIONS AND PRACTICES CONSIDERED

1. Single-agent docetaxel (Taxotere®)
2. Single-agent pemetrexed (Alimta®) plus vitamin supplementation
3. Dose-reduced docetaxel in patients at high risk of hematologic toxicity or with a previous history of febrile neutropenia
4. Erlotinib
5. Gefitinib for selected symptomatic patients

The following were considered, but not recommended:

1. Oral topotecan
2. Combination chemotherapy (docetaxel-based or other)

MAJOR OUTCOMES CONSIDERED

- Survival
- Quality of life
- Tumor response rate
- Symptom control
- Toxicity (adverse effects of treatment)

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
 Hand-searches of Published Literature (Secondary Sources)
 Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The electronic databases, MEDLINE (1996 through November Week 3 2005), EMBASE (1996 through 2005, week 53), and the Cochrane Library (2005, Issue 4), were searched using the search terms detailed in Appendix A of the original guideline document.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO), the European Cancer Conference (ECCO), the European Society for Medical Oncology (ESMO), and the International Association for the Study of Lung Cancer (IASLC) were searched for abstracts of relevant trials published between 2000 and 2005. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>), the National Guideline Clearinghouse (<http://www.guideline.gov/>), and the National Institute for Clinical Excellence (<http://www.nice.org.uk/>) were also searched for existing evidence-based practice guidelines.

The initial literature searches were reviewed by one member of the Disease Site Group (DSG), and articles that did not meet the broad inclusion criteria were excluded (i.e., general review articles, study type or design was not applicable, trials focusing on disease types other than non-small cell lung cancer [NSCLC], trials of first-line therapy, and trials not involving systemic therapy). Two reviewers selected relevant articles and abstracts from the remaining literature, resolving any disagreements on article selection by discussion. The reference lists from the selected articles were searched for additional trials, as were the reference lists from relevant review articles.

Study Selection Criteria

Articles published as full reports or as abstracts were selected for inclusion in this systematic review of the evidence if they focused on second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer, reported outcomes of interest, and were:

1. Systematic reviews or practice guidelines of systemic therapy; or
2. Meta-analyses comparing systemic therapy with best supportive care (BSC) or another systemic therapy; or
3. Randomized trials comparing different systemic therapy agents or regimens, or systemic therapy with best supportive care; or
4. Randomized trials comparing different doses and/or schedules of systemic therapy agents.

The following were excluded from the systematic review of the evidence:

1. Systematic reviews or meta-analyses that pre-dated, or confined their analysis to, trials included in the 2001 practice guideline developed by the Lung Disease Site Group on the role of single-agent docetaxel as second-line treatment for advanced non-small cell lung cancer.
2. Trials that included a mix of untreated and previously treated patients.
3. Articles published in a language other than English.
4. Trials that included less than 50 patients per trial arm. Trials with less than 100 patients were considered underpowered to detect any clinically meaningful difference in effect given the range of typical accrual times, follow up times, and times-to-event. Trials with less than 50 patients per trial arm are reported in Appendix B in the original guideline document and are included in any relevant meta-analyses conducted.

NUMBER OF SOURCE DOCUMENTS

Twenty-five randomized clinical (phase II and III) trials and three evidence-based practice guidelines were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Synthesizing the Evidence

A pooled analysis of mortality data from randomized trials (phase II and III) of weekly versus three-weekly administration of second-line or subsequent single-agent docetaxel was pre-planned. The meta-analysis was conducted on six-month survival data extrapolated from published survival curves, using the Review Manager software, RevMan 4.2.7, available from the Cochrane Collaboration (www.cochrane.org). To limit the potential for error, two researchers independently extrapolated the six-month data from the survival curves, and the average of the two estimates was used in the analysis. However, data censored on the survival curves was not accounted for, which may limit the reliability of the results.

In addition, a post-hoc meta-analysis, also using the Review Manager software, was conducted to explore the impact of a weekly versus three-weekly docetaxel schedule on the incidence of grade 3/4 febrile neutropenia. This analysis was based on the number of patients who reported experiencing an event in each

treatment arm compared with the number of patients who were available for toxicity evaluation. Where not provided, the latter number was assumed to equal the number of patients randomized.

Results of the meta-analyses are expressed as a relative risk or risk ratio with 95% confidence intervals (CI), where relative risk < 1 indicates a benefit for weekly administration of docetaxel and relative risk > 1 suggests a benefit for three-weekly administration. The random-effects model was used for comparative testing of the pooled results across studies in preference to the fixed-effects model, as the more conservative estimate of effect. Sensitivity analyses were also conducted to explore the impact of including data from abstract reports.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Internal Review

Prior to submission of this Evidence-based Series report for external review, the report was reviewed and approved by the Program in Evidence-Based Care (PEBC) Report Approval Panel, which consists of two members including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel were regarding the level of evidence included in the guideline, specifically the inclusion of randomized phase II trials and the section on novel agents. The Panel noted that the level of evidence supporting the recommendation for gefitinib monotherapy as second-line or subsequent treatment was limited. The Panel also suggested that the reporting of response rates be deleted, and the reporting of results of randomized phase II trials be non-comparative. The Lung Disease Site Group (DSG) agreed that the study selection criteria were too broadly defined. Trials with less than 50 patients per treatment arm were excluded from the

guideline and placed in an appendix. Randomized phase II trials were retained for questions for which there was not randomized phase III evidence available and were included in the meta-analyses conducted for dose/scheduling of docetaxel. The section on novel agents was condensed and in future guidelines the Lung DSG will consider excluding novel agents. The Lung DSG explicitly acknowledged the limitations of the evidence for gefitinib recommendation by clarifying the evidence for this recommendation. Response rate data was retained in the guideline as clinical practice relies on the assessment of response as an indication to continue treatment. Text in the results section which compared outcomes between randomized groups of non-comparative phase II trials was revised to be non-comparative. Editorial changes were also made as per the suggestions of the Panel.

External Review

Following review and discussion of sections 1 and 2 of this evidence-based series and review and approval of the report by the PEBC Report Approval Panel, the Lung DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Feedback was obtained through a mailed survey of 129 practitioners in Ontario, including 33 medical oncologists, 32 respirologists, 25 surgeons, 21 radiation oncologists, and 18 other practitioners. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on January 31, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung Disease Site Group reviewed the results of the survey.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Single-agent docetaxel (Taxotere®) at a dose of 75 mg/m² every three weeks is recommended as second-line therapy for patients with recurrent or progressive non-small cell lung cancer (NSCLC) and adequate performance status (0-2).
- Single-agent pemetrexed (Alimta®) at a dose of 500 mg/m² every three weeks is also an option for second-line therapy of recurrent or progressive disease, if available. This chemotherapy should be administered with vitamin supplements: oral folic acid 350-1,000 micrograms daily and intramuscular vitamin B₁₂ 1,000 micrograms every nine weeks, beginning between one to two weeks before, and continuing until three weeks after chemotherapy.
- Oral topotecan at a dose of 2.3 mg/m² administered day 1-5 every three weeks is not recommended for second-line therapy of recurrent or progressive disease.
- Docetaxel administered at a dose of 33.3-40 mg/m² (for six weeks on an eight-week cycle or for three weeks on a four-week cycle) may be considered in patients at high risk of hematologic toxicity or with a previous history of febrile neutropenia using the three-weekly docetaxel schedule.

- Combination chemotherapy (docetaxel-based or other) is not currently recommended as second-line or subsequent therapy for recurrent or progressive disease.
- Erlotinib at a dose of 150 mg/day is recommended as third-line therapy for patients with advanced recurrent or progressive non-small cell lung cancer who maintain a good performance status following previous platinum-based and docetaxel (or pemetrexed) chemotherapy. Erlotinib is also an option for second-line therapy, particularly in patients who are not candidates for chemotherapy or for those with progression after first-line docetaxel-platinum chemotherapy.
- Gefitinib at a dose of 250 mg/day may be considered for second-line and subsequent therapy only for selected symptomatic patients who are not candidates for chemotherapy and for whom erlotinib is not available.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized phase II and III trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- There is evidence from two randomized phase III trials of a significant benefit in overall survival and quality of life (QOL) for single-agent docetaxel when used as second-line therapy for recurrent or progressive non-small cell lung cancer (NSCLC). In one trial, comparing docetaxel at 75 mg/m² to best supportive care (BSC), median survival was increased from 4.6 months to 7.5 months (p=0.01 log rank), and one-year survival from 12% to 37% (p=0.003 chi-square). Treatment with docetaxel was also associated with a significant improvement in patient-related pain compared to best supportive care (p=0.005). In a second trial, comparing docetaxel with vinorelbine or ifosfamide, median survival was not significantly different, but one-year survival was superior for docetaxel at 75 mg/m² (32% versus 19%, p=0.025, chi-square). Although the optimal duration of therapy is unknown, in both trials, treatment with docetaxel was continued until disease progression or development of unacceptable toxicity.
- The results of a single randomized phase III trial suggest a similar survival benefit for single-agent pemetrexed at 500 mg/m², combined with vitamin supplementation, compared to docetaxel at 75 mg/m², when used as second-line therapy. Median survival was 8.3 months for pemetrexed versus 7.9 months for docetaxel, with one-year survival of 29.7% for both treatments. A test for non-inferiority using the percent retention method, indicated that pemetrexed retained >50% of the survival benefit of docetaxel over best supportive care (p=0.047). However, the primary test of non-inferiority, which required that survival for pemetrexed be • 10% worse than docetaxel,

was not statistically significant ($p=0.226$). Hematologic toxicities, including febrile neutropenia, occurred with significantly lower frequency with pemetrexed than with docetaxel. A comparison of QOL measures showed no significant difference between the two treatments.

- The results of a single randomized phase III trial suggest a similar one-year survival rate for oral topotecan at a dose of 2.3 mg/m^2 compared to docetaxel at 75 mg/m^2 , when used as second-line therapy. The one-year survival was 25.1% for topotecan versus 28.7% for docetaxel; however, the overall survival difference approached statistical significance in favour of docetaxel (hazard ratio, 1.16; 95% confidence interval, 1.00-1.35; $p=0.057$), with a median survival of 27.9 weeks and 30.7 weeks for topotecan and docetaxel, respectively. A comparison of QOL measures also significantly favoured docetaxel.
- Evidence from four randomized trials suggests that docetaxel administered weekly at a dose of between 33.3 mg/m^2 and 40 mg/m^2 may achieve similar survival and superior tolerability to docetaxel administered three-weekly at a dose of 75 mg/m^2 . A pooled analysis of six-month survival data from those trials provided a hazard ratio of 0.99 (95% confidence interval, 0.84-1.16, $p=0.91$). The benefit for the weekly regimen in terms of a reduction in the incidence of febrile neutropenia approached statistical significance (hazard ratio, 0.29; 95% confidence interval, 0.08-1.12, $p=0.07$). However, this potential advantage must be weighed against the greater inconvenience to the patient of weekly treatment.
- Docetaxel-based and other combination chemotherapy regimens have yet to be compared to single-agent docetaxel in a fully published randomized phase III trial. The results of several small trials suggest promising activity for some combination regimens, but those regimens will require further testing.
- There is evidence from a single randomized phase III trial of a significant benefit in overall survival and QOL for the epidermal growth factor receptor inhibitor (EGFRI) erlotinib (Tarceva®) when compared to placebo as second or third-line systemic therapy. Median survival was increased from 4.7 months to 6.7 months ($p<0.001$ log rank), and one-year survival from 22% to 31%. Erlotinib was also associated with a significant delay in time to deterioration for cough ($p=0.04$), dyspnea ($p=0.03$) and pain ($p=0.04$), and an improvement in overall physical QOL ($p=0.01$), compared to placebo.
- The results of a single randomized phase III trial revealed no statistically significant survival or QOL benefit for the epidermal growth factor receptor inhibitor gefitinib (Iressa®) when compared to placebo as second-line or subsequent therapy. Gefitinib was associated with a superior tumour response rate (8% vs 1%, $p<0.0001$) and symptom improvement. Two randomized phase II trials suggest that modest tumour response rates and symptom control can be achieved with gefitinib. Although a significant survival benefit has not been demonstrated for this agent in a placebo-controlled study, the trials suggest that gefitinib may provide clinically important symptomatic benefits.

POTENTIAL HARMS

Refer to the original guideline document for common grade 3 or 4 toxicities reported in the trials reviewed.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Noble J, Ellis P, Mackay JA, Evans WK, Lung Cancer Disease Site Group. Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Mar 27. 51 p. (Evidence-based series; no. 7-19). [89 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Jan 17 (revised 2006 Mar 27)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Lung Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All members of the Lung Cancer Disease Site Group disclosed potential conflict of interest information. None of the authors of this systematic review declared any conflicts of interest.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: a clinical practice guideline. Summary. Toronto (ON):

Cancer Care Ontario (CCO), 2006 Mar 27. Various p. (Practice guideline; no. 7-19). Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995; 13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on July 19, 2002. The information was verified by the guideline developer on August 19, 2002. This summary was updated by ECRI on September 9, 2005. The updated information was verified by the guideline developer on October 3, 2005. This summary was updated by ECRI on June 8, 2006. The updated information was verified by the guideline developer on June 26, 2006.

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Date Modified: 10/9/2006